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PTO/SB/05 (4/98)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.	6439.US.01
First Inventor or Application Identifier	John M. Lipari
Title	Novel Formulations Comprising Lipid-Regulating Agents
Express Mail Label No.	EE835515961US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [X] * Fee Transmittal Form *(e.g., PTO/SB/17)*
(Submit an original and a duplicate for fee processing)

2. [X] Specification [Total Pages 10]
(preferred arrangement set forth below)
- Descriptive title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings *(if filed)*
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

3. [ ] Drawing(s) *(35 U.S.C. 113)* [Total Sheets]

4. Oath or Declaration [Total Pages 3]
a. [X] Newly executed (original or copy)
b. [ ] Copy from a prior application (37 C.F.R. § 1.63(d))
(for continuation/divisional with Box 16 completed)
i. [ ] DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R §§ 1.63(d)(2) and 1.33(b).

** NOTE FOR ITEMS 1 & 13 IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).*

ADDRESS TO: **Assistant Commissioner for Patents**
Box Patent Application
Washington, DC 20231

5. [ ] Microfiche Computer Program *(Appendix)*

6. Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
a. [ ] Computer Readable Copy
b. [ ] Paper Copy (identical to computer copy)
c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. [ ] Assignment Papers (cover sheet & document(s))
8. [ ] 37 C.F.R.§3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
9. [ ] English Translation Document *(if applicable)*
10. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
11. [ ] Preliminary Amendment
12. [X] Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
13. [ ] * Small Entity Statement(s) *(PTO/SB/09-12)* [ ] Statement filed in prior application Status still proper and desired
14. [ ] Certified Copy of Priority Document(s)
(if foreign priority is claimed)
15. [ ] Other: .....

16. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment:*
[ ] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No. _____ / _____
Prior application information: *Examiner* _____ *Group / Art Unit:* _____
For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

[ ] *Customer Number or Bar Code Label* *(Insert Customer No. or Attach bar code label here)* or [X] *Correspondence address below*

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Country		Telephone	(847) 937-8272	Fax	(847) 938-2623

Name (Print/Type)	Dugal S. Sickert	Registration No. (Attorney/Agent)	33,784
Signature		Date	12/18/98

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FEE TRANSMITTAL

Patent fees are subject to annual revision on October 1. These are the fees effective October 1, 1997. Small Entity payments must be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB/09-12. See 37 C.F.R. §§1.27 and 1.28.

TOTAL AMOUNT OF PAYMENT ($) 838

Complete if Known	
Application Number	
Filing Date	December 18, 1998
First Named Inventor	John M. Lipari
Examiner Name	
Group / Art Unit	
Attorney Docket No.	6439.US.O1

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 01-0025
Deposit Account Name: Abbott Laboratories

[X] Charge Any Additional Fee Required Under 37 C.F.R. §§ 1.16 and 1.17
[ ] Charge the Issue Fee Set in 37 C.F.R. §1.18 at the Mailing of the Notice of Allowance

2. [ ] Payment Enclosed: [ ] Check [ ] Money Order [ ] Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	790	201	395	Utility filing fee	760
106	330	206	165	Design filing fee	
107	540	207	270	Plant filing fee	
108	790	208	395	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 760

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below		Fee Paid
Total Claims	20	-20** =	0	X		=	0
Independent Claims	4	- 3** =	1	X		=	78
Multiple Dependent						=	0

**or number previously paid, if greater; For Reissues, see below

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	22	203	11	Claims in excess of 20
102	82	202	41	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
109	82	209	41	** Reissue independent claims over original patent
110	22	210	11	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 78

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	0.00
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	0.00
139	130	139	130	Non-English specification	0.00
147	2,520	147	2,520	For filing a request for reexamination	0.00
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	0.00
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	0.00
115	110	215	55	Extension for reply within first month	0.00
116	400	216	200	Extension for reply within second month	0.00
117	950	217	475	Extension for reply within third month	0.00
118	1,510	218	755	Extension for reply within fourth month	0.00
128	2,060	228	1,030	Extension for reply within fifth month	0.00
119	310	219	155	Notice of Appeal	0.00
120	310	220	155	Filing a brief in support of an appeal	0.00
121	270	221	135	Request for oral hearing	0.00
138	1,510	138	1,510	Petition to institute a public use proceeding	0.00
140	110	240	55	Petition to revive - unavoidable	0.00
141	1,320	241	660	Petition to revive - unintentional	0.00
142	1,320	242	660	Utility issue fee (or reissue)	0.00
143	450	243	225	Design issue fee	0.00
144	670	244	335	Plant issue fee	0.00
122	130	122	130	Petitions to the Commissioner	0.00
123	50	123	50	Petitions related to provisional applications	0.00
126	240	126	240	Submission of Information Disclosure Stmt	0.00
581	40	581	40	Recording each patent assignment per property (times number of properties)	0.00
146	790	246	395	Filing a submission after final rejection (37 CFR 1 129(a))	0.00
149	790	249	395	For each additional invention to be examined (37 CFR 1.129(b))	0.00

Other fee (specify) ____________ 0.00

Other fee (specify) ____________ 0.00

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 0.00

SUBMITTED BY

				Complete (if applicable)	
Typed or Printed Name	Dugal S. Sickert			Reg. Number	33,784
Signature	[signature]	Date	12/18/98	Deposit Account User ID	

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Novel Formulations Comprising Lipid-Regulating Agents

Field of the Invention

The present invention relates to novel formulations for oral administration comprising lipid-regulating agents.

Background of the Invention

2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethylester, also known as fenofibrate, is representative of a broad class of compounds having pharmaceutical utility as lipid regulating agents. More specifically, this compound is part of a lipid-regulating agent class of compounds commonly known as fibrates, and is disclosed in U.S. Patent No. 4,058,552.

Fenofibrate has been prepared in several different formulations, c.f., U.S. Patent No. 4,800,079 and U.S. Patent No. 4,895,726. U.S. Patent No. 4,895,726 discloses a co-micronized formulation of fenofibrate and a solid surfactant.

U.S. Patent No. 4,961,890 discloses a process for preparing a controlled release formulation containing fenofibrate in an intermediate layer in the form of crystalline microparticles included within pores of an inert matrix. The formulation is prepared by a process involving the sequential steps of dampening said inert core with a solution based on said binder, then projecting said fenofibrate microparticles in a single layer onto said dampened core, and thereafter drying, before said solution based on said binder dissolves said fenofibrate microparticles, and repeating said three steps in sequence until said intermediate layer is formed.

European Patent Application No. EP0793958A2 discloses a process for producing a fenofibrate solid dosage form utilizing fenofibrate, a surface active agent and polyvinyl pyrrolidone in which the fenofibrate particles are mixed with a polyvinyl pyrrolidone solution. The thus obtained mixture is granulated with an aqueous solution of one or more surface active agents, and the granulate thus produced is dried.

PCT Publication No. WO 82/01649 discloses a fenofibrate formulation having granules that are comprised of a neutral core that is a mixture of saccharose and starch. The

neutral core is covered with a first layer of fenofibrate, admixed with an excipient and with a second microporous outer layer of an edible polymer.

U.S. Patent No. 5,645,856 describes the use of a carrier for hydrophobic drugs, including fenofibrate, and pharmaceutical compositions based thereon. The carrier comprises a digestible oil and a pharmaceutically-acceptable surfactant component for dispersing the oil in vivo upon administration of the carrier, which comprises a hydrophilic surfactant, said surfactant component being such as not to substantially inhibit the in vivo lipolysis of the digestible oil.

Gemfibrozil is another member of the fibrate class of lipid-regulating agents. U.S. Patent No. 4,927,639 discloses a disintegratable formulation of gemfibrozil providing both immediate and sustained release, comprising a tablet compressed from a mixture of a first and second granulation, and a disintegration excipient operable to effect partial or complete disintegration in the stomach. The first granulation comprises finely divided particles of pure gemfibrozil granulated with at least one cellulose derivative, and the second granulation comprises finely divided particles of pure gemfibrozil granulated with a pharmaceutically-acceptable water soluble or insoluble polymer which are then uniformly coated with a pharmaceutically-acceptable (meth)acylate copolymer prior to admixture with the first granulation. The first and second granulations are present in the final composition in a ratio of from about 10:1 to about 1:10.

U.S. Patent 4,925,676 discloses a disintegratable gemfibrozil tablet providing both immediate and enteric release, which is compressed from a mixture of a first granulation of gemfibrozil with at least one acid-disintegratable binder, and a second granulation formed from the first granulation, but regranulated or coated with an alkali-disintegratable formulation of at least one substantially alkali-soluble and substantially acid-insoluble polymer.

Another class of lipid-regulating agents are commonly known as statins, of which pravastatin and atorvastatin are members. U.S. Patents 5,030,447 and 5,180,589 describe stable pharmaceutical compositions, which when dispersed in water have a pH of at least 9, and include a medicament which is sensitive to a low pH environment, such as prevastatin, one or more fillers such as lactose and/or microcrystalline cellulose, one or more binders, such as microcrystalline cellulose (dry binder) or polyvinylpyrrolidone (wet binder), one or more disintegrating agents such as croscarmellose sodium, one or more lubricants such as magnesium stearate and one or more basifying agents such as magnesium oxide.

It is an object of the present invention to provide formulations for oral administration comprising lipid-regulating agents having enhanced bioavailability when compared to commercially available formulations.

Summary of the Invention

The present invention is directed to formulations for oral administration comprising a lipid-regulating agent, further comprising at least one structured lipid as the primary solvent medium for the lipid-regulating agent. One or more emulsifiers may be added to the formulation.

The formulation may be administered directly, diluted into an appropriate vehicle for administration, encapsulated into soft or hard gelatin shells or capsules for administration, or administered by other means obvious to those skilled in the art.

Brief Description of the Drawings

Figure 1 is a graph showing the plasma concentration in fasted dogs of the formulation of Example 1 and a reference composition.

Figure 2 is a graph showing the plasma concentration in fasted dogs of the formulation of Example 2 and a reference composition.

Detailed Description of the Invention

The bulk lipid-regulating agent can be prepared by any available method, as for example the compound fenofibrate may be prepared by the procedure disclosed in U.S. Patent No. 4,058,552 or the procedure disclosed in U.S. Patent No. 4,739,101, both herein incorporated by reference.

Representative structured lipids include, but are not limited to, caprylic/capric/lauric triglycerides, e.g., Captex 350™ (Abitec) and caprylic/capric/linoleic triglycerides, e.g., Captex 810 series (Abitec) and Miglyol 818 (Creanova), and in general, include those lipids containing saturated medium and long-chain fatty acids esterified to the same glycerol molecule. A preferred structured lipid is a caprylic/capric/lauric triglyceride, e.g., Captex 350™ (Abitec).

Suitable emulsifiers include pharmaceutically acceptable surfactants such as, for example, TPGS (d-aalpha Tocopheryl Polyethylene Glycol 1000 Succinate), phospholipids, polyoxyethylene sorbitan fatty acid derivatives, castor oil or hydrogenated castor oil ethoxylates, polyglycerol esters of fatty acids, fatty acid ethoxylates, alcohol ethoxylates, polyoxyethylene-polyoxypropylene co-polymers and block co-polymers. Preferred emulsifiers include polyglycerol esters of fatty acids. A more preferred emulsifier is Caprol 6620, a polyglycerol-6 dioleate (Abitec).

Other optional ingredients which may be included in the compositions of the present invention are those which are conventionally used in oil-based drug delivery systems, e.g. antioxidants such as, for example, tocopherol, ascorbyl palmitate, ascorbic acid, butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, etc.; pH stabilizers such as, for example, citric acid, tartaric acid, fumaric acid, acetic acid, glycine, arginine, lysine, potassium hydrogen phosphate, etc.; thickeners/suspending agents such as, for example, hydrogenated vegetable oils, beeswax, colloidal silicon dioxide, gums, celluloses, silicates, bentonite, etc.; flavoring agents such as, for example, cherry, lemon, aniseed flavors, etc.; sweeteners such as aspartame, saccharin, cyclamates, etc.; and co-solvents such as, for example, ethanol, propylene glycol, dimethyl isosorbide, etc.

The solution comprising the lipid-regulating agent is prepared by dissolving said agent in the structured lipid with adequate mixing at or about room temperature. If an emulsifier is used, it is added to the structured lipid with mixing prior to addition of the lipid-regulating agent.

The resulting premix liquid comprising the lipid-regulating agent may be dosed directly for oral administration, diluted into an appropriate vehicle for oral administration, filled into soft or hard gelatin capsules for oral administration, or delivered by some other means obvious to those skilled in the art. The premix liquid can be used to improve the oral bioavailability, and/or increase the solubility of said agent.

The invention will be understood more clearly from the following non-limiting representative examples.

Example 1

Miglyol 818 (Creanova) (8.3 gm)was added to a scintillation vial. Caprol 6G20 (polyglycerol-6 dioleate) (Abitec) (1.0 gm) was added to the vial and mixed until uniform. Fenofibrate (Sigma) (0.7 gm) was then added to the vial and mixed until it was completely dissolved. 957 mg. of the premix (containing 67 mg. fenofibrate) was added to each of six soft gelatin capsules using a syringe. The capsules were heat sealed and stored.

Example 2

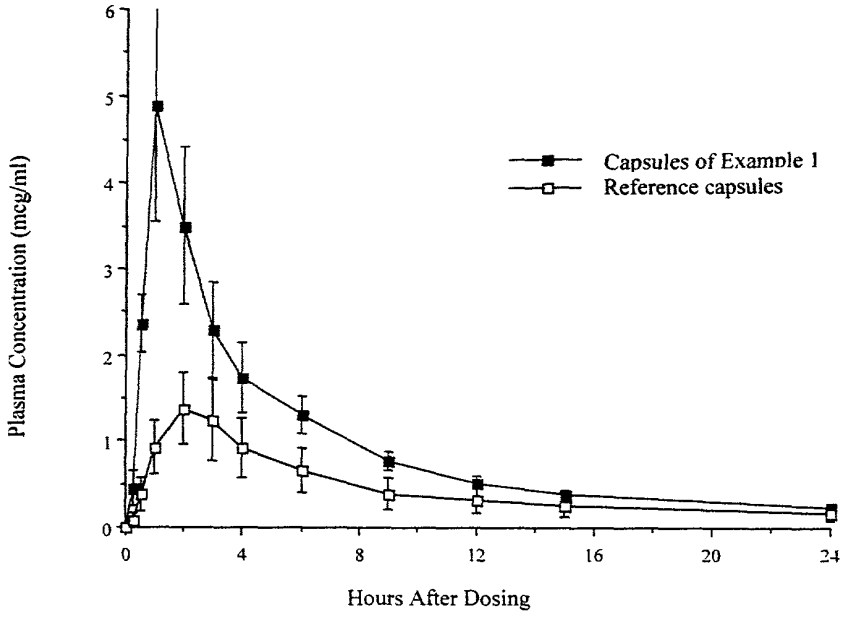
Miglyol 818 (Creanova)(9.3 gm) was added to a scintillation vial. Fenofibrate (Sigma) (0.7 gm) was added to the Miglyol and mixed until completely dissolved. 957 mg. of the premix (containing 67 mg. fenofibrate) was added to each of six soft gelatin capsules using a syringe. The capsules were heat sealed and stored.

Example 3

Capsules prepared by the process described in Example 1 and 2, and from a commercial fenofibrate composition, Lipanthyl 67M (Groupe Fornier) (Reference), were each administered to a group of fasted dogs at a dose of 67 mg/dog (one capsule per dog). The plasma concentrations of fenofibric acid were determined by HPLC. Concentrations were normalized to a 6.7 mg/kg dose in each dog. Figures 1 and 2 present the resulting data in graph form.

Figure 1

Mean (±SEM, n=6) Plasma Concentrations of Fenofibric Acid after a 67 mg Capsule Dose of Fenofibrate in Fasted Dogs



Note: 67 mg dose administered to n=6 dogs; concentrations normalized to a 6.7 mg/kg dose.

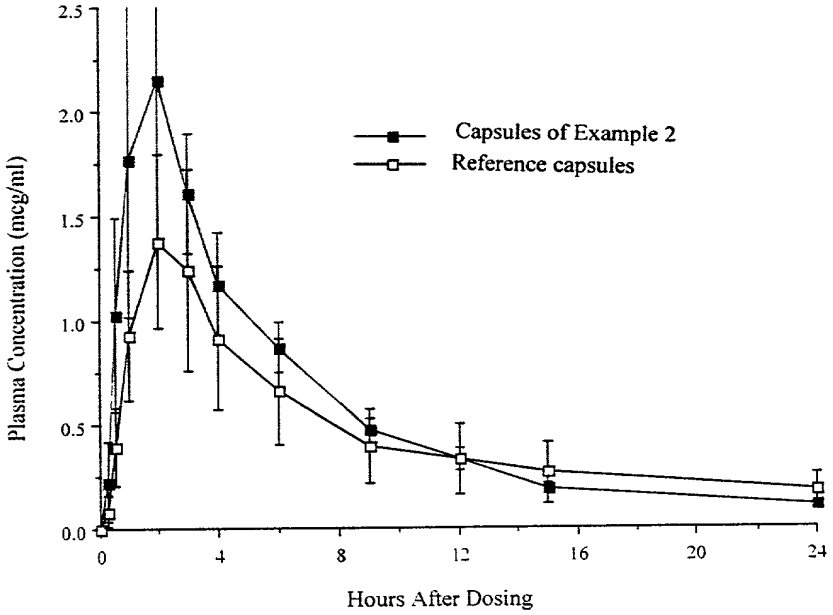
The results, provided as mean ± SD, n = 6 were as follows:

Lipanthyl 67M (reference):
Cmax = 1.88 ± 0.97 mcg/ml
Tmax = 1.6 ± 0.9 hr
$t_{1/2}$ = 4.5 hr
AUC (0-24) = 11.08 ± 9.42 mcg•hr/ml
F(%) = 21.1 ± 11.8

Capsules of Example 1:
Cmax = 5.13 ± 3.12 mcg/ml
Tmax = 1.0 ± 0.5 hr
$t_{1/2}$ = 6.9 hr
AUC (0-24) = 23.62 ± 10.61 mcg•hr/ml
F(%) = 49.1 ± 21.9

Figure 2

Mean (±SEM, n=6) Plasma Concentrations of Fenofibric Acid after a 67 mg Capsule Dose of Fenofibrate in Fasted Dogs



Note: 67 mg dose administered to n=6 dogs; concentrations normalized to a 6.7 mg/kg dose.

The results, provided as mean ± SD, n = 6 were as follows:

Lipanthyl 67M (reference):
Cmax = 1.88 ± 0.97 mcg/ml
Tmax = 1.6 ± 0.9 hr
$t_{1/2}$ = 4.5 hr
AUC (0-24) = 11.08 ± 9.42 mcg•hr/ml
F(%) = 21.1 ± 11.8

Capsules of Example 2:
Cmax = 2.56 ± 1.90 mcg/ml
Tmax = 1.8 ± 0.8 hr
$t_{1/2}$ = 5.4 hr
AUC (0-24) = 13.47 ± 6.62 mcg•hr/ml
F(%) = 27.9 ± 13.6

Claims

1. A composition comprising a lipid-regulating agent dissolved in at least one structured lipid.

2. A composition of claim 1 wherein the lipid-regulating agent is a fibrate.

3. A composition of claim 2 wherein the fibrate is fenofibrate.

4. A composition of claim 1 wherein at least one or more of the structured lipids is selected from caprylic/capric/lauric triglycerides and caprylic/capric/linoleic triglycerides.

5. A composition of claim 4 wherein the structured lipid is a caprylic/capric/lauric triglyceride.

6. A composition of claim 1 further comprising at least one emulsifier.

7. A composition of claim 6 wherein at least one emulsifier is selected from a polyglycerol ester of a fatty acid.

8. A composition of claim 7 wherein the polyglycerol ester of a fatty acid is a polyglycerol-6 dioleate.

9. A composition of claim 1 that contains a therapeutically-effective amount of a lipid-regulating agent.

10. A composition of claim 9 wherein the lipid-regulating agent is a fibrate.

11. A composition of claim 10 wherein the fibrate is fenofibrate.

12. A capsule comprising a composition of claim 1.

13. A capsule of claim 12 wherein the lipid regulating agent is a fibrate.

14. A capsule of claim 13 wherein the fibrate is fenofibrate.

15. A method of treating hyperlipidemia comprising the administration of a composition of claim 1 to a patient.

16. A method of treating hyperlipidemia comprising the administration of a composition of claim 9 to a patient.

17. A method of claim 16 wherein the lipid-regulating agent is a fibrate.

18. A method of claim 17 wherein the fibrate is fenofibrate.

19. A composition of claim 1 further comprising at least one co-solvent.

20. A composition of claim 19 wherein at least one co-solvent is selected from ethanol, propylene glycol, and dimethyl isosorbide.

Abstract

The present invention is directed to a formulation comprising a lipid-regulating agent dissolved in at least one structured lipid as the primary solvent medium for said agent. One or more emulsifiers may be added to the formulation.

PATENT
IN THE UNITED STATES PATENT & TRADEMARK OFFICE

APPLICANT: J. M. Lipari, et al.

SERIAL NO.: (not yet assigned)

FILED: December 18, 1998

FOR: NOVEL FORMULATIONS COMPRISING LIPID-REGULATING AGENTS

EXAMINER: (not yet assigned)

CASE NO.: 6439.US.O1

GROUP ART UNIT: (not yet assigned)

DATE: December 18, 1998

Express Mail No.: EE835515961US

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as U.S. Express Mail, Post Office to Addressee Service under 37 C.F.R. 1.10 addressed to:

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C.

Date of Deposit: December 18, 1998

Kathleen T. Litz 12/18/98
Kathleen T. Litz Date

DECLARATION AND POWER OF ATTORNEY FOR A UNITED STATES PATENT APPLICATION

As a below-named inventor, I hereby declare:

My residence, post office address and citizenship are as stated below next to my name. I believe I am an original and first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled NOVEL FORMULATIONS COMPRISING LIPID-REGULATING AGENTS, the specification of which is attached.

I hereby state that I have reviewed and understand the contents of the above-mentioned specification, including the claims.

I acknowledge a duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, 1.56.

Claim to benefit of foreign application(s) as follows:

I hereby claim foreign priority benefits under 35 U.S.C. '119 for the following foreign applications for patent or inventors certificate.

NONE

The following foreign applications for patent or inventor's certificate have a filing date earlier than the filing date of the applications identified above.

NONE

Claim to benefit of earlier U.S. application(s) as follows:

I hereby claim the benefit under 35 U.S.C.'120 of the following earlier-filed United States patent applications. Insofar as the subject matter of each of the claims of this application is not disclosed in the prior U.S. applications in the manner required by 35 U.S.C. '112, first paragraph, I acknowledge a duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. '1.56 which came into existence between the filing date(s) of the prior applications and the national or PCT filing date of this application.

NONE

I hereby appoint the following Attorneys and/or agents to prosecute this application and any continuation or divisional applications based hereon, and to transact all business in the Patent and Trademark Office connected therewith:

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Residence:	Gages Lake, Illinois 60030
Citizenship:	United States of America

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that all statements made herein were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

John M. Lipari	Date	Dawn M. Raymond	Date
Tom Reiland	Date		